

SEQUENCE LISTING

<110> WOULFE, SUSAN L.
JAIN, RITA
BURR, AIMEE

<120> ENGINEERED FAB' FRAGMENT ANTI-TUMOR
NECROSIS FACTOR ALPHA IN COMBINATION WITH DISEASE MODIFYING
ANTI-RHEUMATIC DRUGS

<130> 122294-1010

<140>

<141> 2003-12-05

<150> US 60/431,053

<151> 2002-12-05

<160> 40

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 CDRH1

<400> 1

Asp Tyr Gly Met Asn

1

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<211> 17

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<220>

<223> hTNF40/human hybrid CDRH2

<400> 2

Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val Lys

1

5

10

15

Gly

<210> 3

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> hTNF40 CDRH3

<400> 3

Gly Tyr Arg Ser Tyr Ala Met Asp Tyr

1

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<211> 11

<212> PRT

<213> Artificial Sequence

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<223> hTNF40 CDRL1

<400> 4

Lys Ala Ser Gln Asn Val Gly Thr Asn Val Ala

1

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<211> 7

<212> PRT

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<223> hTNF40 CDRL2

<400> 5

Ser Ala Ser Phe Leu Tyr Ser

1

5

<210> 6

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> hTNF40 CDRL3

<400> 6

Gln Gln Tyr Asn Ile Tyr Pro Leu Thr

1

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<210> 7

<211> 17

<212> PRT

<213> Artificial Sequence

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<223> hTNF40 CDRH2

<400> 7

Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Val Asp Asp Phe Lys
 1 5 10 15
 Gly

<210> 8
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 <221> CDS

<222> (1)...(321)
 <223> hTNF40-gL1

<223> hTNF40-gL1

<400> 8
 gac att caa atg acc cag agc cca tcc agc ctg agc gca tct gta gga 48
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 gac cgg gtc acc atc act tgt aaa gcc agt cag aac gta ggt act aac 96
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
 20 25 30
 gta gcc tgg tat cag caa aaa cca ggt aaa gcc cca aaa gcc ctc atc 144
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
 35 40 45
 tac agt gcc tct ttc ctc tat agt ggt gta cca tac agg ttc agc gga 192
 Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Ser Gly
 50 55 60
 tcc ggt agt ggt act gat ttc acc ctc acg atc agt agc ctc cag cca 240
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 gaa gat ttc gcc act tat tac tgt caa cag tat aac atc tac cca ctc 288
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
 85 90 95
 aca ttc ggt cag ggt act aaa gta gaa atc aaa 321
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 11
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<220>
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 <222> (1)...(354)

<223> gh3hTNF40.4

<223> Grafted Heavy Chain for Modified Fab

<400> 11

gag gtt cag ctg gtc gag tca gga ggc ggt ctc gtg cag cct ggc gga	48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly	
1 5 10 15	
tca ctg aga ttg tcc tgt gct gca tct ggt tac gtc ttc aca gac tat	96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Val Phe Thr Asp Tyr	
20 25 30	
gga atg aat tgg gtt aga cag gcc ccg gga aag ggc ctg gaa tgg atg	144
Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met	
35 40 45	
ggt tgg att aat act tac att gga gag cct att tat gct gac agc gtc	192
Gly Trp Ile Asn Thr Tyr Ile Gly Glu Pro Ile Tyr Ala Asp Ser Val	
50 55 60	
aag ggc aga ttc acg ttc tct cta gac aca tcc aag tca aca gca tac	240
Lys Gly Arg Phe Thr Phe Ser Leu Asp Thr Ser Lys Ser Thr Ala Tyr	
65 70 75 80	
ctc caa atg aat agc ctg aga gca gag gac acc gca gtg tac tat tgt	288
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	
85 90 95	
gct aga gga tac aga tct tat gcc atg gac tac tgg ggc cag ggt acc	336
Ala Arg Gly Tyr Arg Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr	
100 105 110	
cta gtc aca gtc tcc tca	354
Leu Val Thr Val Ser Ser	
115	

<210> 83

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework L1

<400> 83

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	
1 5 10 15	
Asp Arg Val Thr Ile Thr Cys	
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<210> 84

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework L1

<400> 84

Asp	Ile	Val	Met	Thr	Gln	Ser	Gln	Lys	Phe	Met	Ser	Thr	Ser	Val	Gly
1				5				10						15	
Asp	Arg	Val	Ser	Val	Thr	Cys									
				20											

<210> 85

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework L2

<400> 85

Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	Tyr
1				5				10						15

<210> 86

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework L2

<400> 86

Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Ala	Leu	Ile	Tyr
1				5				10						15

<210> 87

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework L3

<400> 87

Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5				10						15	
Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys
				20				25					30		

<210> 88

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework L3

<400> 88

Gly	Val	Pro	Tyr	Arg	Phe	Thr	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr
1				5				10					15		
Leu	Thr	Ile	Ser	Thr	Val	Gln	Ser	Glu	Asp	Leu	Ala	Glu	Tyr	Phe	Cys
			20					25					30		

<210> 89

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework L4

<400> 89

Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg
1				5				10		

<210> 90

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework L4

<400> 90

Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg
1				5				10		

<210> 91

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework H1

<400> 91

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr		
			20					25					30		

<210> 92

<211> 30

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework H1

<400> 92

Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Thr	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Val	Phe	Thr		
			20					25					30		

<210> 93

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework H2

<400> 93

Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	Gly
1				5					10				

<210> 94

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework H2

<400> 94

Trp	Val	Lys	Gln	Ala	Pro	Gly	Lys	Ala	Phe	Lys	Trp	Met	Gly
1				5					10				

<210> 95

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework H3

<400> 95

Arg	Val	Thr	Ile	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr	Met	Glu
1				5					10					15	
Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg
			20					25					30		

<210> 96

<211> 32

<212> PRT

<213> Artificial Sequence

<220>

<223> hTNF40 framework H3

<400> 96

Arg	Phe	Ala	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser	Thr	Ala	Phe	Leu	Gln
1				5				10					15		
Ile	Asn	Asn	Leu	Lys	Asn	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	Ala	Arg
			20					25					30		

<210> 97

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework H4

<400> 97

Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser
1				5				10		

<210> 98

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> human group 1 consensus framework H4

<400> 98

Trp	Gly	Gln	Gly	Thr	Thr	Leu	Val	Thr	Val	Ser	Ser
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<210> 99

<211> 324

<212> DNA

<213> murine

<220>

<221> CDS

<222> (1)...(324)

<223> mouse hTNF40 light chain variable domain

<400> 99

gac	att	gtg	atg	acc	cag	tct	caa	aaa	ttc	atg	tcc	aca	tca	gta	gga	48
Asp	Ile	Val	Met	Thr	Gln	Ser	Gln	Lys	Phe	Met	Ser	Thr	Ser	Val	Gly	
1				5				10					15			

gac	agg	gtc	agc	gtc	acc	tgc	aag	gcc	agt	cag	aat	gtg	ggt	act	aat	96
Asp	Arg	Val	Ser	Val	Thr	Cys	Lys	Ala	Ser	Gln	Asn	Val	Gly	Thr	Asn	
			20					25					30			

gta	gcc	tgg	tat	caa	cag	aaa	cca	gga	caa	tct	cct	aaa	gca	ctg	aat	144
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Val	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ser	Pro	Lys	Ala	Leu	Asn	
	35						40					45				
tac	tcg	gca	tcc	ttc	cta	tat	agt	gga	gtc	cct	tat	cgc	ttc	aca	ggc	192
Tyr	Ser	Ala	Ser	Phe	Leu	Tyr	Ser	Gly	Val	Pro	Tyr	Arg	Phe	Thr	Gly	
	50					55				60						
agt	gga	tct	ggg	aca	gat	ttc	act	ctc	acc	atc	agc	act	gtg	cag	tct	240
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Thr	Val	Gln	Ser	
	65				70					75					80	
gaa	gac	ttg	gca	gag	tat	ttc	tgt	cag	caa	tat	aac	atc	tat	cct	ctc	288
Glu	Asp	Leu	Ala	Glu	Tyr	Phe	Cys	Gln	Gln	Tyr	Asn	Ile	Tyr	Pro	Leu	
				85					90					95		
acg	ttc	ggg	gct	ggg	acc	aag	ctg	gag	ctg	aaa	cgt					324
Thr	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg					
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<210> 100
 <211> 354
 <212> DNA
 <213> murine

<220>
 <221> CDS
 <222> (1)...(354)
 <223> mouse hTNF40 heavy chain variable domain

<400> 100																
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Gln	Ile	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Leu	Lys	Lys	Pro	Gly	Glu	
1				5				10					15			
aca	gtc	aag	atc	tcc	tgc	aag	gct	tct	gga	tat	gtt	ttc	aca	gac	tat	96
Thr	Val	Lys	Ile	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Val	Phe	Thr	Asp	Tyr	
			20					25					30			
gga	atg	aat	tgg	gtg	aag	cag	gct	cca	gga	aag	gct	ttc	aag	tgg	atg	144
Gly	Met	Asn	Trp	Val	Lys	Gln	Ala	Pro	Gly	Lys	Ala	Phe	Lys	Trp	Met	
		35					40					45				
ggc	tgg	ata	aac	acc	tac	att	gga	gag	cca	ata	tat	gtt	gat	gac	ttc	192
Gly	Trp	Ile	Asn	Thr	Tyr	Ile	Gly	Glu	Pro	Ile	Tyr	Val	Asp	Asp	Phe	
	50					55					60					
aag	gga	cga	ttt	gcc	ttc	tct	ttg	gaa	acc	tct	gcc	agc	act	gcc	ttt	240
Lys	Gly	Arg	Phe	Ala	Phe	Ser	Leu	Glu	Thr	Ser	Ala	Ser	Thr	Ala	Phe	
	65				70					75					80	
ttg	cag	atc	aac	aac	ctc	aaa	aat	gag	gac	acg	gct	aca	tat	ttc	tgt	288
Leu	Gln	Ile	Asn	Asn	Leu	Lys	Asn	Glu	Asp	Thr	Ala	Thr	Tyr	Phe	Cys	
				85					90					95		
gca	aga	ggg	tac	cgg	tcc	tat	gct	atg	gac	tac	tgg	ggg	caa	gga	acc	336
Ala	Arg	Gly	Tyr	Arg	Ser	Tyr	Ala	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	

100	105	110	
tca gtc acc gtc tct tca			354
Ser Val Thr Val Ser Ser			
115			

<210> 101
 <211> 84
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Ompa oligonucleotide adaptor

<221> CDS
 <222> (29)...(0)
 <223> 67

<400> 101	
tcgagttcta gataacgagg cgtaaaaaat gaaaaagaca gctatcgcaa ttgcagtggc	60
cttggctctg acgtacgagt cagg	84

<210> 102
 <211> 67
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> CDS
 <222> (2)...(40)

<221> CDS
 <222> (43)...(66)

<223> IGS cassette-1

<400> 102	
g agc tca cca gta aca aaa agt ttt aat aga gga gag tgt ta atg aag	48
Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Met Lys	
1 5 10 15	

aag act gct ata gca att g	67
Lys Thr Ala Ile Ala Ile	
20	

<210> 103
 <211> 69
 <212> DNA
 <213> Artificial Sequence

<220>
 <221> CDS
 <222> (2)...(43)

<221> CDS

<222> (45)...(68)

<223> IGS cassette-2

<400> 103

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g agc tca cca gta aca aaa agt ttt aat aga ggg gag tgt taa      43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  *
    1              5              10
```

```
a atg aag aag act gct ata gca att g      69
  Met Lys Lys Thr Ala Ile Ala Ile
    15              20
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<210> 104

<211> 81

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (2)...(43)

<221> CDS

<222> (57)...(80)

<223> IGS cassette-3

<400> 104

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g agc tca cca gta aca aaa agc ttt aat aga gga gag tgt tga      43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  *
    1              5              10
```

```
ggaggaaaaa aaa atg aag aaa act gct ata gca att g      81
          Met Lys Lys Thr Ala Ile Ala Ile
            15              20
```

<210> 105

<211> 81

<212> DNA

<213> Artificial Sequence

<220>

<221> CDS

<222> (2)...(43)

<221> CDS

<222> (57)...(80)

<223> IGS cassette-4

<400> 105

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g agc tca cca gta aca aaa agt ttt aat aga gga gag tgt tga      43
  Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys  *
    1              5              10
```

cgaggattat ata atg aag aaa act gct ata gca att g
 Met Lys Lys Thr Ala Ile Ala Ile
 15 20

81

<210> 106
 <211> 30
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> human group 3 consensus framework H1

<400> 106
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
 20 25 30

<210> 107
 <211> 14
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> human group 3 consensus framework H2

<400> 107
 Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
 1 5 10

<210> 108
 <211> 32
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> human group 3 consensus framework H3

<400> 108
 Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
 1 5 10 15
 Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
 20 25 30

<210> 109
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> human group 3 consensus framework H4

<400> 109

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10

<210> 113

<211> 214

<212> PRT

<213> Artificial Sequence

<220>

<223> CDP870 Light chain mature protein sequence

<400> 113

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
35 40 45
Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Tyr Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ile Tyr Pro Leu
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205
Phe Asn Arg Gly Glu Cys
210

<210> 115

<211> 229

<212> PRT

<213> Artificial Sequence

<220>

<223> CDP870 Heavy chain mature protein sequence

<400> 115

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Val Phe Thr Asp Tyr


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atacagatct tatgccatgg actactgggg ccagggtacc ctagtccacag tctcctcagc 1140
ttccaccaag ggcccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg 1200
cacagcggcc ctgggctgcc tgggtcaagga ctacttcccc gaaccgggtga cgggtgctgtg 1260
gaactcaggc gccctgacca gcggcgtgca caccttcccc gctgtcctac agtcctcagg 1320
actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagacctt 1380

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catctgcaac gtgaatcaca agcccagcaa caccaagggtc cacaagaaaag ttgagcccaa 1440
atcttgtgac aaaactcaca catgcgccgc gtgatga 1477

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<210> 117

<211> 1477

<212> DNA

<213> Artificial Sequence

<220>

<223> CDP870 nucleic acid sequence (anti-sense strand)

<400> 117

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ggagggcacg gtcaccacgc tgctgagggg gtagagtcct gaggactgta ggacagccgg 180
gaaggtgtgc acgccgctgg tcagggcgcc tgagttccac gacaccgtca ccggttcggg 240
gaagtagtcc ttgaccaggc agcccagggc cgctgtgccc ccagagggtgc tcttggagga 300
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accctggccc cagtagtcca tggcataaga tctgtatcct ctgacacaat agtacactgc 420
ggtgtcctct gctctcaggc tattcatttg gaggtatgct gttgacttgg atgtgtctag 480
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aatccaaccc atccattcga ggccctttcc cggggcctgt ctaacccaat tcattccata 600
gtctgtgaag acgtaaccag atgcagcaca ggacaatctc agtgatccgc caggctgcac 660
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